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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/594,876

09/29/2006

Hannsjorg Sinn

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EXAMINER

RUSSEL, JEFFREY E

ART UNIT

PAPER NUMBER

1654

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/594,876	<b>Applicant(s)</b> SINN, HANNSJORG	
	<b>Examiner</b> Jeffrey E. Russel	<b>Art Unit</b> 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 09 April 2009.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,3-8,12,13,15 and 20-22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-8,12,13,15 and 20-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 September 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>20090409</u> .  | 6) <input type="checkbox"/> Other: _____                          |

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1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 9, 2009 has been entered.

2. Claims 1, 3-8, 12, 13, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The methotrexate:albumin molar ratio range recited at claim 1, line 5, and particularly that portion of the range embracing methotrexate:albumin molar ratios of less than 1:1, is unclear. Because there are not, e.g., 1000 potential conjugation sites in a methotrexate molecule, it is not possible to conjugate 1000 molecules of albumin to 1 molecule of methotrexate (in order to achieve a methotrexate:albumin molar ratio of 1:1000).

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 1, 3-8, 12, and 13 are rejected under 35 U.S.C. 103(a) as being obvious over the Wolff et al abstract (Blood, Vol. 102, No. 11, page 404b) in view of Dave et al (U.S. Patent No. 6,491,923) and the Stehle et al article (Anti-Cancer Drugs, Vol. 8, pages 677-685). The Wolff et al abstract teaches the use of methotrexate-human serum albumin conjugates to prevent experimental acute GVHD in rats who have undergone bone marrow transplantation. Bone marrow cells and spleen T-cells are transplanted from other rats, i.e. are allogeneic transplants. With respect to instant claim 5, because the Wolff et al abstract teaches administering the same active agents according to the same method steps to the same subjects as are claimed by

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Applicant, inherently chronic GVHD will be prevented in the method of the Wolf et al abstract to the same extent claimed by Applicant. The Wolff et al abstract does not teach a methotrexate-albumin molar ratio for the conjugates. Dave et al teach that it is a matter of routine experimentation to determine the molar ratio of components in a conjugate in order to optimize biological activity and conjugate stability. See, e.g., column 9, lines 44-51. The Stehle et al article teaches that for i.v.-administered methotrexate-albumin conjugates, higher methotrexate:albumin molar ratios result in more rapid uptake of the conjugates by the liver and removal from the circulation. For this reason, conjugates with a 1:1 molar ratio of methotrexate:albumin are preferred. See, e.g., page 683, column 2, first full paragraph, and page 683, column 1, first full paragraph. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal methotrexate-albumin molar ratios for the conjugates of the Wolff et al abstract, because Dave et al and the Stehle et al teach that component ratio is an art-recognized result-effective variable which is routinely determined and optimized in the conjugate arts. Further, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use methotrexate-albumin molar ratios closer to 1:1 for the conjugates of the Wolff et al abstract, because the Stehle et al article teaches that such molar ratios help to minimize rapid uptake of the conjugate by the liver and its removal from circulation.

5. Claims 15, 20, and 22 are rejected under 35 U.S.C. 103(a) as being obvious over Sutton et al (U.S. Patent No. 5,993,805) in view of the European Patent Application 0 282 057 or Low et al (U.S. Patent No. 5,688,488). Sutton et al teach adding EDCI to a solution of methotrexate, stirring to ensure initiation and complete activation of the methotrexate, and then adding HSA,

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whereby the methotrexate is bound to amine residues on the HSA. See, e.g., Example 12. Sutton et al teach reacting methotrexate with EDCI in solution, but do not specify the solvent. The European Patent Application '057 teaches activating methotrexate with EDCI for reacting with an antibody carrier, wherein the activation reaction is carried out in dry DMF. Low et al teach that folic acid (of which methotrexate is an analog) can be activated by EDC in a DMSO solution. The activated folic acid is then reacted with a protein, ribonuclease. See, e.g., column 18, lines 47-50. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to perform the activation reaction of Sutton et al using the dry DMF solvent of the European Patent Application '057 or the DMSO solvent of Low et al, because the European Patent Application '057 teaches that dry DMF is a known solvent for performing the activation reaction of Sutton et al, because Low et al teach that DMSO is a known solvent for performing the activation reaction of a compound analogous to methotrexate, and because substitution of one known reaction solvent for another with only the expected result that methotrexate is activated by EDCI is prima facie obvious. With respect to the "activated by heating" step recited in claim 20, the claim does not specify any particular degree of heating. However, Applicant's specification at page 8, lines 36-37, states that activation can occur at temperatures ranging from 10°C to 100°C, which embraces room temperatures. Sutton et al do not disclose a temperature for their step of reacting methotrexate with EDCI, and therefore it is presumed to occur at room temperature and satisfies Applicant's claim limitation. In any event, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal temperatures for Sutton et al's step of reacting methotrexate with EDCI, because reaction temperature is an art-recognized result-effective

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variable which is routinely determined and optimized in the chemical arts. Sutton et al do not teach a molar ratio of methotrexate and albumin reactants of from 10:1 to 1:10, or of from 1.5:1 to 1:1.5. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to determine all operable and optimal molar ratios for the methotrexate and albumin reactants of Sutton et al, because reactant ratio is an art-recognized result-effective variable which is routinely determined and optimized in the chemical arts.

6. Applicant's arguments filed April 9, 2009 have been fully considered but they are not persuasive.

The examiner maintains his position for the reasons of record. Applicants cite to the Stehle et al article (Anti-Cancer Drugs, Vol. 8, pages 677-685) as showing that high molar ratios of methotrexate to albumin can lead to denaturation of albumin in methotrexate-albumin conjugates, and that only if albumin is present in a native form can it act as a transporter and transport the active substance with which it is loaded to the desired effective site. Firstly, Applicant's claims do not require the conjugated albumin to be in native form. Patentability must be based upon claimed, not unclaimed, differences over the prior art. Secondly, the Stehle et al article is prior art against Applicants' claims, and has been applied in combination with the Wolff et al abstract under 35 U.S.C. 103(a) in the rejection of Applicants' method of preventing claims. The teachings of Stehle et al provide motivation and suggestion to use methotrexate and albumin in molar ratios closer to 1:1 for the conjugates of the Wolff et al abstract, in order to avoid the negative results taught by the Stehle et al article, e.g., rapid uptake of the conjugate by the liver and its removal from circulation. Thirdly, using Applicants' argument that only if albumin is present in a native form can it act as a transporter and transport the active substance

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with which it is loaded to the desired effective site (see, e.g., page 8, lines 8-9, of the Remarks), then it must be concluded that the albumin present in the methotrexate-albumin conjugates of the Wolff et al abstract is present in a native form, because the methotrexate-albumin conjugates of the Wolff et al abstract are effective to prevent GVHD and therefore must have been transported to the desired effective site.

Applicant summarizes the state of the art as assuming that loading of albumin with a high dosage of therapeutically active agents is necessary in order to achieve a therapeutic response (see, e.g., page 7, last paragraph, and page 10, lines 2-4, of the Remarks). The examiner does not agree with this summary. Applicant's summary might reflect the state of the art at the time the Stehle et al article was published, in 1997 (see especially the paragraph bridging pages 677 and 678 of the Stehle et al article). However, Applicant's invention was made in 2004 or 2005, at least 7 years after the publication of the Stehle et al article, and the teachings of the Stehle et al article form part of the state of the art at the time Applicants' invention was made. The benefits of Applicant's molar ratios appear to be expected, rather than unexpected, in view of the teachings of the Stehle et al article.

With respect to instant claims 15, 20, and 22, note that these claims specify a methotrexate:albumin reactant ratio, and do not specify a ratio of methotrexate:albumin in the conjugate product of the reaction. The teachings of the Stehle et al article are not relevant to the ratios recited in the claims drawn to the method for preparing a conjugate.

7. Claim 21 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The Wolff et al abstract (Blood, Vol. 102, No. 11,

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page 404b), applied above, is limited to the allogeneic transplantation of bone marrow cells and spleen T-cells, and is not deemed to anticipate or render obvious Applicant's claim drawn to kidney, heart, or liver transplantation.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:00 A.M. to 5:30 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (571) 272-0562. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jeffrey E. Russel/  
Primary Examiner, Art Unit 1654

JRussel  
May 4, 2009